

Substance use in pregnancy: The medical challenge

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Abstract

Substance use contributes significantly to the global burden of disease. Growing numbers of women use nicotine, alcohol, and illicit substances. Women are the most vulnerable to problematic substance use in their reproductive years. The first 1000 days of life, starting at conception, have been established as a critical window of time for long-term health and development. Substance use in pregnancy is associated with negative pregnancy and child health outcomes. The impact of antenatal substance use on these outcomes needs to be considered within a challenging and complex context. This review provides an overview of the current literature on the impact of substances on pregnancy and child outcomes as well as the evidence and guidelines on screening and interventions for women using substances during pregnancy.

Keywords

High-risk pregnancy, drugs (abuse), complications, maternal-fetal medicine

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Introduction

Substance use disorders are a significant, preventable contributor to the global burden of disease. According to the United Nations Office on Drugs and Crime 2017 report, cannabis remains the most common illicit drug used globally followed by amphetamines.² Opioids cause the highest negative health impact, and many people are poly drug users.² Biological, psychosocial, and cultural factors lead to sex and gender differences in the prevalence, patterns, and experiences of substance use.³⁻⁶ While men currently have higher prevalence rates of substance use disorders, the gender gap is narrowing with growing numbers of women using nicotine, alcohol, and illicit substances. Once women start using substances, they increase their rate of use more rapidly and progress more quickly to substance use disorders than men.² Women are at greatest risk of developing a substance use disorder in their reproductive years with the highest prevalence rates seen in adolescence and early adulthood.8

According to a 2013 national survey in the United States of America (USA), the rate of cigarette use in pregnancy was 15.4%, alcohol use 9.4%, and illicit substance use 5.4%. In Australia, alcohol is the most commonly used drug in pregnancy. Findings from a

population-based cohort revealed that 27% of Australian women drank in the first trimester, and 27% continued to drink alcohol at some level during pregnancy. 11 In other studies, 13.8% of Australian women reported cigarette smoking in the first 20 weeks of pregnancy, 12 and 5% of women screened were using cannabis and 2% other illicit drugs in pregnancy. 13 There is limited information on the prevalence of substance use in pregnancy in low- and middleincome countries. In a South African survey among pregnant women, 19.6% of women tested positive for alcohol and 8.8% positive for at least one drug (methamphetamine, cannabis, Mandrax).¹⁴ While a study using self-report measures found that 36.8% of women smoked cigarettes, 20.2% used alcohol and 4% used illicit substances at the time of their first antenatal visit.15 High rates of polysubstance use have been

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shown in pregnant women using substances.^{16–18} The rates of comorbid cigarette smoking are particularly high in pregnant women using substances, and poly substance users have even higher odds of smoking.¹⁹

The first 1000 days of life, starting at conception, have been established as a critical window of time for long-term health and development. 20,21 It is therefore crucial to understand the impact substance use has on pregnancy, breastfeeding, maternal—infant bonding, and child outcomes. This review provides an overview of the current literature on the impact of substances on pregnancy and child outcomes as well as the evidence and guidelines on screening and interventions for women using substances during pregnancy. This is a broad review of most substances used in pregnancy and is aimed at the general obstetrician and obstetric medicine specialist.

The impact of substances on pregnancy and child outcomes

Risk factors for problematic substance use in pregnancy include past alcohol, nicotine or illicit drug use, unintended pregnancy, lower level of education, unemployment, younger age, comorbid physical and mental health problems, childhood trauma, environmental stress, intimate partner violence, easy access to substances, and lack of knowledge of the impact of substances on fetal development.^{22–25}

Globally, 41% of all pregnancies are unintended which means that many women use substances before they become aware of their pregnancy.²⁶ Substance use itself increases the risk of unintended pregnancy.²⁷ For many women, pregnancy is a motivation to stop using substances, to cut back on their use, or to engage with harm reduction services such as opioid substitution programmes.²⁸ However, the chronic and relapsing nature of substance use disorders means that some women are unable to stop using in pregnancy. For those who manage to achieve abstinence during pregnancy, the rates of relapse in the first six months postpartum are high.²⁹ In a prospective USA study, 83% of women (N=152) achieved abstinence to at least one substance in pregnancy, but in the postpartum period, 80% relapsed to at least one substance.²⁹

Pregnant women with substance use disorders are less likely to receive antenatal care than pregnant women not using substances. ^{30,31} Barriers to accessing antenatal care include the impact of underlying medical and psychiatric comorbidities, poor coping skills, transport and child care difficulties, intimate partner violence, incarceration, poor provider communication, stigmatization, fear of being reported to the police, losing child custody or other legal consequences, and

negative health belief factors such as having an external locus of control, lack of belief in the efficacy of health care, and lack of trust in health care providers. 32–34 In addition to poor antenatal care, substance using women also carry burdens of psychiatric and medical comorbidities and negative psychosocial environments. This context makes it challenging to determine the impact an individual drug has on pregnancy and child outcomes. Factors that influence pregnancy and child outcomes in substance using mothers include the dose, duration, and pattern of substance use, exposure to multiple substances, inadequate prenatal care, poor nutrition, medical comorbidities, psychiatric comorbidities, intimate partner violence, poor maternal—infant bonding, and chaotic postnatal environments. 37–51

In spite of the complexity of the context within which peripartum substance use takes place, it is known that substances of abuse have negative effects on maternal physiology and readily cross the placenta impacting on fetal development and brain growth. ⁵² An overview of the effects of alcohol, nicotine, cannabis, opioids, cocaine, and methamphetamine on pregnancy and child outcomes is provided below.

Alcohol

Alcohol is a well-established teratogen, and fetal alcohol spectrum disorders (FASD) are globally the leading known form of preventable birth defects and developmental disabilities.⁵³ Findings from a recent meta-analysis report that eight out of 1000 in the general population have FASD and that one of every 13 pregnant women who consumed alcohol during pregnancy delivered a child with FASD.⁵⁴ The amount, timing, and pattern of drinking may impact FASD outcomes.⁵⁵ Alcohol use in pregnancy is associated with other long-term negative child outcomes including growth deficits,⁵⁶ behavior problems,^{57,58} and cognitive and motor deficits.^{52,59} Heavy alcohol use is associated with negative pregnancy outcomes such as stillbirth,⁶¹ low birth weight,⁶² miscarriage, 60 small-for-gestational age,⁶² preterm delivery,⁶³ and infant mortality.64 Findings regarding pregnancy outcomes for low or very low alcohol intake are mixed. 65,66

Women receive conflicting messages regarding how much alcohol is safe during pregnancy. ⁶⁷ Animal models demonstrate that all stages of embryonic development are vulnerable to the teratogenic effects of alcohol ⁶⁸ and that even low levels of alcohol exposure impact brain development. ⁶⁹ Given the well-established risk of teratogenicity and the potential negative long-term child outcomes even at low levels of consumption, ^{57,70} no amount of alcohol use in pregnancy can be considered safe. Most guidelines recommend

abstinence in pregnancy, and health practitioners should give a consistent message regarding abstinence. $^{71-74}$

Nicotine

Nicotine is the primary psychoactive component of tobacco, and it passes readily through the placenta.⁷⁵ Cigarettes contain many harmful products, and animal studies have shown that nicotine itself is toxic for the developing brain.⁵² In rodent studies, prenatal and early postnatal nicotine exposure interfered with catecholamine and brainstem autonomic nuclei development and altered development of the neocortex, hippocampus, and cerebellum. Animal models also show defective metabolic, reproductive, respiratory, and cardiovascular outcomes in nicotine-exposed offspring, suggesting that nicotine alone may be responsible for many of the negative long-term health outcomes in exposed offspring. 77 Prenatal nicotine exposure in humans is associated with increased risk of orofacial clefting and potentially a range of other congenital anomalies. 78 Cigarette smoking also negatively impacts child health outcomes. Neonates are at increased risk of infections,⁷⁹ cochlear dysfunction,⁸⁰ sudden infant death syndrome, 81 and infant mortality. 82,83 Longerterm negative child outcomes include poorer cognitive development,⁸⁴ behavior problems,^{85,86} childhood obesity, 87 hypertension, diabetes, and respiratory complications.⁸⁸ In a recent review, Holbrook⁷⁸ concludes that prenatal nicotine exposure has multiple, irreversible, negative impacts on child health, scholastic achievement, and behavior. Cigarette smoking is associated with multiple negative pregnancy outcomes including miscarriage, 89 ectopic pregnancy, 90,91 preterm premature rupture of membranes, 92 abruptio placentae, 93 placenta praevia, 94 intrauterine growth restriction, 95 small-for-gestational age, 96,97 preterm delivery, 98 low birth weight, 95,96,98 stillbirth, and perinatal death. 98,99 The amount and timing of smoking may impact on these negative outcomes with greater amounts and continuous smoking throughout pregnancy having worse outcomes. 97-99 Stopping smoking in pregnancy is associated with improved pregnancy and child health outcomes including reductions in the incidence of low birth weight, preterm birth, and intensive care unit (ICU) admissions. 100 Interestingly, cigarette smoking in pregnancy reduces the risk of preeclampsia, but the other negative consequences clearly outweigh the benefit of any potential risk reduction. 101

Some women view electronic nicotine delivery systems (ENDS) as safer than cigarettes and therefore potential harm reduction tools in pregnancy. However, the research on the safety and efficacy of ENDS in pregnancy is lacking. 104,105 The World

Health Organization (WHO) cautions pregnant women against the use of ENDS because of the potential long-term consequences for fetal brain development. Hos Many women also report using ENDS as an aid to smoking cessation during pregnancy. Hos Yet, a recent systematic review and meta-analysis of ENDS in nonpregnant patients concluded that there is very limited evidence on the impact of ENDS on smoking reduction or cessation. Hos

Cannabis

Cannabis is lipophilic; it readily crosses the placental barrier¹⁰⁹ and impacts on fetal brain development.¹¹⁰ Many women perceive cannabis to be safe in pregnancy.¹¹¹ However, cannabis has teratogenic potential, and its use is associated with anencephaly¹¹² and adverse effects on neurodevelopment.¹¹³ Negative child outcomes include smaller head circumferences,¹¹⁴ learning and cognitive problems (particularly executive function deficits),^{115–119} depression,¹²⁰ aggression, and behavior problems.^{115,121} Negative pregnancy outcomes associated with cannabis use include low birth weight,^{122–124} small-for-gestational age,¹²³ preterm delivery,^{124,125} stillbirth,¹²⁶ and placement in neonatal ICUs.^{122,124}

There is growing use of medical cannabis for a range of health conditions including pregnancy-associated hyperemesis. 127 However, the safety of medical cannabis in pregnancy has not yet been established. 113 The American College of Obstetricians and Gynecologists (ACOG) advises that pregnant women and women planning pregnancy should discontinue medical cannabis and rather use agents with better pregnancy-specific safety data. 128

Opioids

Opioids used in pregnancy include heroin and prescription opioids. USA studies have shown an increase in antenatal maternal opioid use in the last decade with a fivefold corresponding increase in neonatal abstinence syndrome (NAS). 129,130 Currently, no strong teratogenic effect has been demonstrated for opioids, while there is uncertainty about a possible weak effect for synthetic opioids on cardiovascular defects. 131 Additional negative child health outcomes associated with opioid exposure include sudden infant death syndrome, 132,133 postnatal growth deficiency, and cognitive and neurobehavioral problems. 52,134 Maternal opioid use is associated with increased risk of maternal death during hospitalization. 135 Negative pregnancy outcomes include intrauterine growth restriction, 135,136 oligohydraminos, 135 low birth weight, 137 preeclampsia, 131 placental insufficiency and abruption, 135 premature

rupture of membranes, ¹³⁵ preterm labour, ^{135,136} post-partum hemorrhage, ¹³⁸ and stillbirth. ^{135,136}

Neonates are at risk of NAS with exposure to illicit and prescription opioids. ^{139,140} Longer and late exposure to prescription opioids increases the risk of NAS. ¹³⁹ NAS presents clinically with tremors, irritability, excessive crying, diarrhea, and seizures. ¹⁴⁰ Rates of nicotine use are high in opioid-using women, and cigarette smoking is associated with greater negative pregnancy outcomes ¹⁴¹ and delay and worsening of NAS. ¹⁴²

Cocaine

Cocaine causes a catecholamine surge, and use in pregnancy has been associated with significant maternal morbidity including hypertensive crisis, myocardial infarction, cerebrovascular events, pulmonary edema, aortic dissection, and renal failure. 143,144 Human and animal studies show teratogenic potential including cardiac, central nervous system, genitourinary, gastrointestinal, and limb malformations. 145–150 Other long-term negative child health outcomes include growth restriction, 151 neurodevelopmental and behavior problems, and cognitive deficits in language and executive function. 152,153 The negative pregnancy outcomes associated with cocaine use include preterm premature rupture of membranes, 154 preeclampsia, placental abruption and infarction, 155 preterm birth, 156 low birth weight, 156 small-for-gestational age, 156 and intrauterine death. 157

Methamphetamine

Methamphetamine exposure has not been shown to be directly teratogenic. Exposed infants are however more likely to be growth restricted, to have difficulty feeding, and to require ICU admission. There is also an increased risk of neonatal and infant death. There is limited data on the longer-term child outcomes of methamphetamine exposure in pregnancy. Children may be at risk for developmental and behavioral effects and cognitive problems. Negative pregnancy outcomes associated with methamphetamine use include low birth weight, shorter gestational age, for preterm birth, for preeclampsia, preeclampsia, for gestational hypertension, for placental abruption, for and intrauterine death.

Screening for substance use in pregnancy

Expert panels and organization guidelines recommend universal screening for substance use in pregnancy. There are several barriers to routine screening including resource limitations and health care provider attitudes. Health providers often hold stigmatizing views of women who use substances in pregnancy. The US Centers for Disease Control

and Prevention Expert Meeting on Perinatal Illicit Drug Use concluded that screening for substance use in pregnancy should be done at the first antenatal visit and repeated at least every trimester for women who screened positive. ¹⁶⁹ They also recommend annual screening for nicotine, alcohol, and illicit drug use as part of routine well-woman care. ¹⁶⁹ The WHO Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy recommend asking about substance use as early as possible in pregnancy and at every antenatal visit. ⁷²

Screening instruments that have been used in pregnancy include the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), 177 Takenumber of drinks, Annoyed, Cut-down, Eye-Opener (T-ACE), 178 Tolerance, Worried, Eye-Opener, Amnesia, Kut down (TWEAK), 179 Substance Use Risk Profile-Pregnancy (SURP-P), 180 Past, Present, Parents, Partner (4P's Plus), 181 Cut-down, Annoyed, Guilt, Eye-Opener (CAGE), 182 Short Michigan Alcohol Screening Test (SMAST), 183 Normal drinker, Eye-Opener, Tolerance (NET), 184 Alcohol Use Disorder Identification Test (AUDIT), ¹⁸⁵ and Alcohol Use Disorder Identification Test-Consumption (AUDIT-C). 186 In a 2010 systematic review of brief screening questionnaires used to identify problem drinking in pregnancy, the T-ACE, TWEAK, and AUDIT-C had high sensitivity and specificity, while the CAGE and SMAST performed poorly.¹⁸⁷

Screening can also be done by asking standard questions during an interview. Open-ended questions may be more likely to lead to disclosure of substance use. 169,171 Either way, screening for substance use in pregnancy needs to be done in a nonjudgmental manner. Women may only feel comfortable disclosing once they have established rapport with their clinician. A positive screen does not imply a diagnosis but does encourage further discussion around health behaviors and consideration of further management. 188

Drug testing should only be done with the consent of the woman and if it is clinically indicated as part of an overall management plan. Urine drug screening is the method of choice when testing for substance use is indicated. 171

Interventions

Pregnant women are more likely to need treatment for substance use compared to nonpregnant women, but they are less likely to receive any. ¹⁸⁹ Interventions for substance using pregnant women should be individualized based on the woman, her context, and the available resources. ⁷² The Screening, Brief Intervention and Referral to Treatment (SBIRT) model is a

cost-effective primary care model that has been recommended in pregnancy. 169,190 When screening reveals substance use, pregnant women should be offered brief interventions and referred for more focused interventions as needed. 72,169 All women should be given information on the risks associated with substance use in pregnancy.

For women needing referral for treatment of substance use in pregnancy, the ideal is to offer collaborative care with addiction, mental health, and social services. Programmes with combined prenatal care and substance use or mental health treatments have shown improved outcomes such as decreased prenatal substance use and decreased need for assisted ventilation at birth. ^{191–193} If possible, services should be offered at a single location with coordinated care. Where appropriate, the woman's partner should be involved in treatment and referred for intervention if needed.

Psychosocial interventions

There are only a few effective therapies for the treatment of substance use during pregnancy. 194 Brief interventions include psychoeducation, counseling, and motivational interviewing techniques. 190 A 2015 Cochrane review of psychosocial interventions for pregnant women in outpatient illicit drug programmes included nine studies of contingency management and five studies of motivational interviewing-based interventions. 195 The authors conclude that current evidence does not show improved outcomes and that better evidence is needed to evaluate psychosocial interventions. 195 In contrast, a 2017 review of psychosocial interventions for smoking in pregnancy found highquality evidence for the effectiveness of counseling, feedback. 100 incentive-based interventions. and Women who received psychosocial interventions had a 17% reduction in low birth weight infants and 22% reduction in neonatal ICU admissions. 100 Reviews on psychosocial interventions for alcohol use have concluded that there are limitations in the amount and quality of available evidence and little evidence to support intervention effectiveness. ^{196–198} In South Africa, the country with the highest global prevalence rates of FASD,⁵⁴ motivational interviewing,¹⁹⁹ communitybased educational interventions, ²⁰⁰ and case management interventions²⁰¹ have been successful in reducing drinking in pregnancy and rates of FASD.

Pharmacological interventions

Alcohol. The safety and efficacy of medications used for alcohol dependence have not been established in pregnancy. Detoxification may be indicated for women using heavy amounts of alcohol. The timing of detoxification should be based on risk assessment

of continued alcohol exposure to the fetus.²⁰⁴ Rapid alcohol withdrawal may lead to fetal distress and death so is best done as an in-patient with close obstetric and medical supervision. ²⁰² The data on the use of benzodiazepines for alcohol withdrawal in pregnancy are limited and conflicting.²⁰³ Disulfiram, an acetyl dehydrogenase inhibitor, causes a severe reaction when combined with alcohol, and its use may put pregnant women at risk.²⁰³ There are also conflicting reports on teratogenicity following first trimester exposure. 205,206 Its use in pregnancy is not currently recommended.²⁰⁷ The nonselective opioid receptor antagonist naltrexone has been shown to reduce the rates of heavy drinking in the nonpregnant population, but there are currently no published studies for the treatment of alcohol use disorders in pregnant women. 203 Studies in opioid-using mothers have not found negative effects on birth outcomes or increased rates of fetal anomalies, but data are lacking, and further studies are needed. 208-210 Acamprosate modulates glutamatergic neurotransmission, and it is effective in maintaining abstinence following detoxification in the nonpregnant population.²¹¹ There are currently no studies in pregnant women.

Nicotine. The safety and efficacy of pharmacological interventions for nicotine smoking have not yet been established.²¹² A 2015 Cochrane review of nicotine replacement products found no evidence that nicotine replacement therapy (NRT) had positive or negative impact on birth outcomes but that they may promote health development outcomes in infants. 104 Å review by Bruin et al. 77 concludes that although human data on the long-term effects of NRT are lacking, there is sufficient evidence from animal models to suggest that many negative long-term developmental effects can be attributed to nicotine alone. A recent ACOG committee opinion advises that NRT be closely supervised and only initiated after a discussion about the known risks of continued smoking versus nicotine replacement.²¹³ NRT should be only be used with a clear decision to stop smoking.²¹³ Intermittent products such as gums should be used at the lowest doses. 202 There are ongoing studies assessing the partial nicotinic acetylcholine receptor agonist varenicline and the antidepressant bupropion for smoking cessation in pregnancy. Small studies of varenicline's safety in pregnancy have not found teratogenicity, but data are lacking. 104,214 Likewise, there is limited data on bupropion, but it has no known risk of fetal anomalies. 215-218 In a recent small randomized placebo-controlled trial, bupropion increased smoking cessation rates and decreased craving, but there were no differences in abstinence rates at the end of pregnancy.219

Opioids. Medication-assisted withdrawal from opioids reduces fetal exposure to opioids but is not recommended because of high rates of opioid relapse rates and increased adverse outcomes.²²⁰ Pregnant women using opioids are best managed with opioid maintenance treatment. 221,222 ACOG discourages the use of medically assisted withdrawal if maintenance treatments are available.²²³ Both methadone and buprenorphine treatment have been shown to significantly improve maternal, fetal, and neonatal outcomes.²²¹ A randomized control trial comparing methadone and buprenorphine showed that infants exposed to buprenorphine had shorter treatment for NAS, required lower doses of morphine, and had shorter hospital stays.²²⁴ However, methadone is superior in retaining women in treatment.²²⁵ Compared to methadone, buprenorphine has lower retention rates with flexibly delivered and low fixed doses but is equally effective when fixed medium or high doses are used.²²⁵ Both methadone and buprenorphine cross the placental barrier and have been shown to impact pregnancy outcomes, fetal neurodevelopmental behavior, and long-term child outcomes. 52,226,227 A 2013 Cochrane review concluded that there is currently insufficient data to recommend one treatment over the other.²²⁸ Naltrexone is used as a treatment for relapse prevention, but use in pregnancy is not currently advised as detoxification is required and more research is needed in pregnant women.²²⁹

Cannabis and stimulants. For cannabis and stimulants, medications are not routinely required for withdrawal. There are currently no recommended pharmacological interventions for cannabis and stimulant use in pregnancy. ¹⁹⁴

Conclusions

Substance use is prevalent in women of reproductive age. Substance use disorders need to be conceptualized as chronic, relapsing conditions that will have an impact on women and families during pregnancy and the postpartum period. All pregnant women and women planning pregnancy should be screened for problematic substance use. Women also need to be screened for psychiatric and medical comorbidities.

Pregnancy is an important opportunity to engage with substance using women. Early antenatal care should be encouraged and the method and frequency of antenatal monitoring determined by the presence of complications such as intrauterine growth restriction. Tailored, safe, and acceptable substance use treatments should be implemented early on. Brief interventions should be offered first followed by more intensive, targeted treatments as needed. Where resources allow,

collaborative care with mental health or addiction services should be offered. Given the high rates of relapse, long-term care is required with assertive outreach and relapse prevention strategies. More research is needed on pharmacological treatment options for substance using pregnant women.

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